Serial Assessment of Strut Coverage of Biodegradable Polymer Drug-Eluting Stent at 1, 2, and 3 Months After Stent Implantation by Optical Frequency Domain Imaging: The DISCOVERY 1TO3 Study (Evaluation With OFDI of Strut Coverage of Terumo New Drug Eluting Stent With Biodegradable Polymer at 1, 2, and 3 Months)

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Serial Assessment of Strut Coverage of Biodegradable Polymer Drug-Eluting Stent at 1, 2, and 3 Months After Stent Implantation by Optical Frequency Domain Imaging

The DISCOVERY 1TO3 Study (Evaluation With OFDI of Strut Coverage of Terumo New Drug Eluting Stent With Biodegradable Polymer at 1, 2, and 3 Months)

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Background—To assess the vessel-healing pattern of Ultimaster drug-eluting stent using optical frequency domain imaging. Our hypothesis is that biodegradable polymer-based drug-eluting technology allows complete very early strut coverage.

Methods and Results—The DISCOVERY 1TO3 study (Evaluation With OFDI of Strut Coverage of Terumo New Drug Eluting Stent With Biodegradable Polymer at 1, 2, and 3 Months) is a prospective, single-arm, multicenter study. A total of 60 patients with multivessel disease requiring staged procedure at 1 month were treated with Ultimaster. Optical frequency domain imaging was acquired at baseline, 1, 2, and 3 months. The primary end point is optical frequency domain imaging–assessed strut coverage at 3 months. Mean age of patients was 67.2±9.9 years, and 73.3% were male, and 36.7% presented with acute coronary syndrome. A total of 132 lesions were treated, with average 1.4 lesions per patient treated at baseline and 1.1 lesions treated at 1 month. Strut coverage at 3 months of single implanted stents (n=71, primary end point) was 95.2±5.2% and of combined single and overlapped stents was 95.4±4.9%. Strut coverage of combined single and overlapped stents at 1 (n=49) and 2 months (n=38) was 85.1±12.7% and 87.9±10.8%, respectively. The median neointimal hyperplasia thickness was 0.04, 0.05, and 0.06 mm, whereas mean neointimal hyperplasia obstruction was 4.5±2.4%, 5.2±3.4%, and 6.6±3.3% at 1, 2, and 3 months, respectively.

Conclusions—Nearly complete strut coverage was observed in this complex population very early after implantation of Ultimaster drug-eluting stent.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT01844843.

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Key Words: coronary artery disease ■ drug-eluting stents ■ hyperplasia ■ neointima ■ percutaneous coronary intervention

First-generation drug-eluting stents (DESs) implantation has been associated with increased risk of late stent thrombosis (ST) and very late ST.[1] A delayed healing response with slower strut coverage compared with bare-metal stents was identified as the main mechanism of late ST and very late ST[2] leading to the recommendation for prolonged duration of dual antiplatelet therapy (DAPT).[3] Among the drug/polymer/stent platform triad that constitutes a DES, the polymer has been the principal culprit of late ST and very late ST[4] because of the lack of the biocompatibility of polymers used in first-generation DES. However, interaction of drug (paclitaxel or sirolimus) on the luminal side of strut with endothelial cell proliferation and strut thickness can play a role in delayed healing patterns. Development of DES with bioabsorbable polymers and abluminal coatings has been associated[5,6] with a decline in ST risk compared with first-generation DES and has led to shorter DAPT recommendation in the newest guidelines.[7]

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WHAT IS KNOWN

- Evaluation of strut coverage using light-based intravascular imaging has been proposed as a surrogate end point for vessel-healing quantification; however, the time course of early (<3 months) strut coverage with new generation drug-eluting stent has not yet been thoroughly analyzed.

WHAT THE STUDY ADDS

- The original design of the present study confirms the ability of optical frequency domain imaging to quantify progressive strut coverage, showing almost full process at 3 months, with an already high rate of coverage at 1 month.
- Current data will serve as a basis for a large randomized clinical trial assessing the safety of abbreviated antiplatelet therapy in recipients of this drug-eluting stent.

The recent development of light-based intravascular imaging with the improved resolution of optical frequency domain imaging (OFDI) was associated with increased capability to evaluate both acute stent implantation results[8] and late healing process including late malapposition,[9] vessel remodeling, and strut coverage.[10,11] OFDI has thus emerged as excellent tool to evaluate the time course of strut coverage.

Development of a new reduced dose sirolimus-eluting stent using a gradient abluminal bioabsorbable coating process on a thin-strut platform (Ultimaster; Terumo, Tokyo, Japan) has a potential to obtain a different strut coverage than early generation of bioabsorbable polymer-based DES.[12–14] The objective of our study is to assess the vessel-healing pattern of Ultimaster DES using OFDI.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design

The DISCOVERY 1TO3 study (Evaluation With OFDI of Strut Coverage of Terumo New Drug Eluting Stent With Biodegradable Polymer at 1, 2, and 3 Months) is a prospective, single-arm, multicenter, open-label study conducted at 5 European sites. The trial was sponsored by Terumo Europe. The sponsor approved the trial protocol, which was developed by the steering committee, and main outline is available in the Data Supplement. The sponsor had no role in analysis and interpretation of the data. The ethics committees at each site and competent authorities of all participating countries approved the study. All patients signed informed consent approved by ethics committees.

Study Stent

The Ultimaster coronary stent has been described in details in previous reports.[12] The study device is a cobalt-chromium bare-metal stent (platform) with thin struts (80 μm) coated with sirolimus (3.9 μg/mm stent length) in a bioresorbable, Poly (DLlactide-co-caprolactone) polymer (PDLLA/PCL=90/10) matrix. The thin biocompatible, bioresorbable gradient coating was chosen to optimize performance with minimal drug and polymer content and controlled drug release kinetics. A reduced drug dose was possible because of an abluminal coating, which ensures an equal amount of drug delivered to the target tissue. Furthermore, coating only the abluminal surface leaves the luminal side of the stent free from drug and polymer. Within 3 to 4 months, the polymer is fully metabolized, and the full dose of the drug is released.

Study Population

A total of 60 complex patients with multivessel disease, requiring staged procedure at 1 month and agreeing to undergo an invasive follow-up at 3 months, were treated with the Ultimaster stent. OFDI imaging was acquired at baseline, 1, 2, and 3 months, and analysis was performed by independent core laboratories (Figure 1). Details of the design and study schedule are provided in the Data Supplement.

The main inclusion criterion is patients with multivessel disease requiring staged procedure within 1 month after baseline (with exception of Germany where staged procedure was allowed at 3 months to comply with regulatory requirements). The main exclusion criteria are patients with ST-segment–elevation myocardial infarction, cardiogenic shock, renal failure (GFR<45 mL/min), left main stenosis >50%, heavily calcified lesions, bifurcations requiring 2 stents, and aorto-ostial lesions. The complete major inclusion/exclusion criteria for the trial are reported in the Data Supplement.

OFDI Procedure and Analysis

The Fastview catheter (Terumo Corp, Tokyo, Japan) was positioned distally to the target segment with the tip ≈1.5 cm distal to the region of interest. The position of the Fastview catheter was documented by cineangiography in an overlap-free, nonforeshortened view of the target vessel. The automatic injector filled with flash media (ie, contrast or mixture with saline) was connected to the standard y-piece of the guiding catheter. After confirming correct position of the Fastview catheter by fluoroscopy and that the guiding catheter is selectively engaged into the ostium of the coronary artery by fluoroscopy, the artery was cleared from blood by automatic injection of flash media at a flow rate of 4 to 5 mL/s. After sufficient clearance of the artery, the automated pullback was started at a speed of 20 mm/s with a frame rate of 160 frames/s. The pullback was stopped after visualization of the complete coronary segment. OFDI images were acquired with commercially available frequency domain system from Lunawave (Terumo Corp). OFDI image analysis was performed using a dedicated offline review system by the Core laboratory. Stented segments were analyzed by an independent analyst blinded to time point after DES implantation. All pullbacks were validated by a second analyst. Cross sections with side branches or poor quality of OFDI images were excluded from this analysis. Lumen and stent areas were drawn in each analyzed cross section, and the derived incomplete stent apposition or neointimal hyperplasia areas were calculated as appropriate. The neointimal hyperplasia thickness was determined based on automated measurements performed from the center of the luminal surface of each strut blooming and its distance to the lumen contour.[9] An uncovered strut was defined as having a neointimal hyperplasia thickness of 0 mm.[9] A malapposed strut was defined as a distance between the center reflection of the strut and the vessel wall greater than strut thickness (bioresorbable polymer sirolimus-eluting stent [BP-SES], 0.80 μm).[15]

End Points

The primary end point of the DISCOVERY 1TO3 study is OFDI-assessed percentage of stent strut coverage at 3 months postprocedure in single implanted stents, with the hypothesis of <20% uncovered stent struts. Secondary end points include strut coverage at 1 and 2 months, percentage of acquired malapposed struts, neointimal hyperplasia thickness and obstruction at 1, 2, or 3 months, and 1-year clinical outcomes. DAPT was recommended for minimum 6 months. (Detailed end point definitions are given in the Data Supplement.) The clinical end points were defined according to the Academic Research Consortium.[16] Analyses of clinical end points were based on events adjudicated by the Clinical Event Committee. Data from

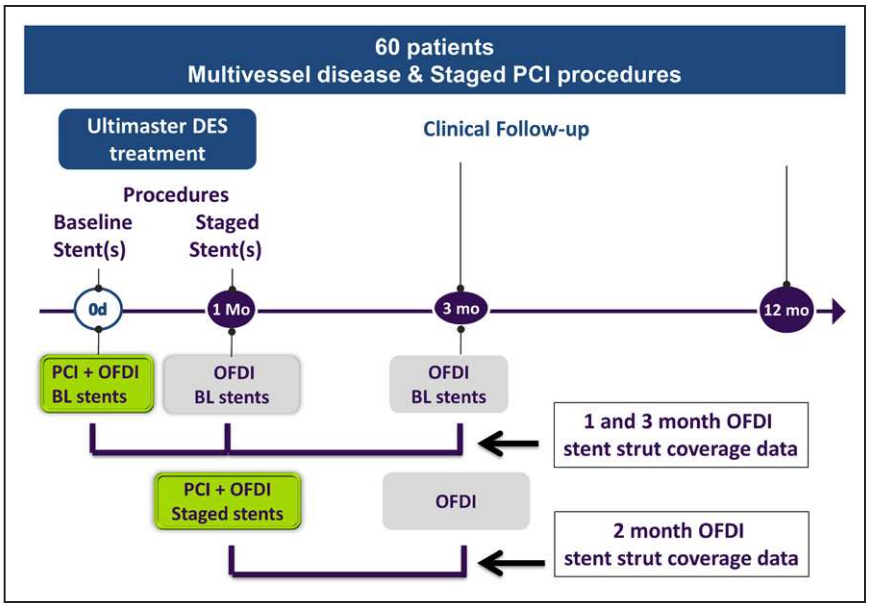

Figure 1. Study design: 60 patients with multivessel disease have been included in the study. Staged procedure is scheduled at 1 month, and optical frequency domain imaging (OFDI) is acquired at baseline, 1, 2, and 3 months. DES indicates drug-eluting stent.

the angiographic and OFDI core laboratories (Centre Europeen De Recherche Cardiovasculaire, Massy, France; CRC, Sao Paulo, Brazil) were used in the analyses.

Table 1. Baseline Characteristics

Baseline Patient Characteristics	n=60 Patients*
Age, y (mean±SD)	67.2±9.9
Sex, males (%)	73.3
Diabetes mellitus (%)	23.3
Hypertension (%)	63.3
Dyslipidemia (%)	67.8
Family history of CAD (%)	30.0
Current smoker (%)	13.6
Previous PCI (%)	26.7
Previous CABG (%)	3.3
Previous MI (%)	21.7
Angina status (%)	
Stable patients	56.7
ACS	36.7
Moderate renal insufficiency GFR or MDRD=45–60), (%)	20.0
Baseline lesion characteristics*	
Vessels diseased	2.2±0.5
Lesions detected	3.2±1.6
Lesions treated—baseline	1.4±0.6
Lesions treated—staged procedure at 1 mo (37 patients)	1.1±0.4
Total lesions treated	2.1±0.7
Stents implanted per lesion	1.2±0.4
Implanted stent length per lesion, mm	22.0±10.9
Implanted stent length per patient, mm	50.4±21.4

ACS indicates acute coronary syndrome.
*One patient withdrew consent.

Statistical Analyses

Statistical analysis was performed in treated population. Continuous data are reported as mean±SD, and categorical variables are reported as number and percentage of patients. One sample *t* test with 95% upper confidence limit was performed to test whether the primary end point is <20%. Nonparametric tests (Wilcoxon signed-rank test) were used for the comparison of continuous variables with dependent time relationship. For the primary lesions (postprocedure, 1-month, and 3-month follow-up), the mixed-effects model was used for the longitudinal analysis of continuous variables considering a gamma distribution with logarithmic link function. We used paired *t* test was used for QCA analysis with $P<0.05$ (2-sided) considered to be statistically significant. All analyses were performed using SAS software, version 9.1 (SAS Institute).

Results

A total of 60 patients were randomized. Mean age of patients was 67.2±9.9 years, 73.3% were male, 30.0% had a previous PCI or CABG, 23.3% had diabetes mellitus, 63.3% had

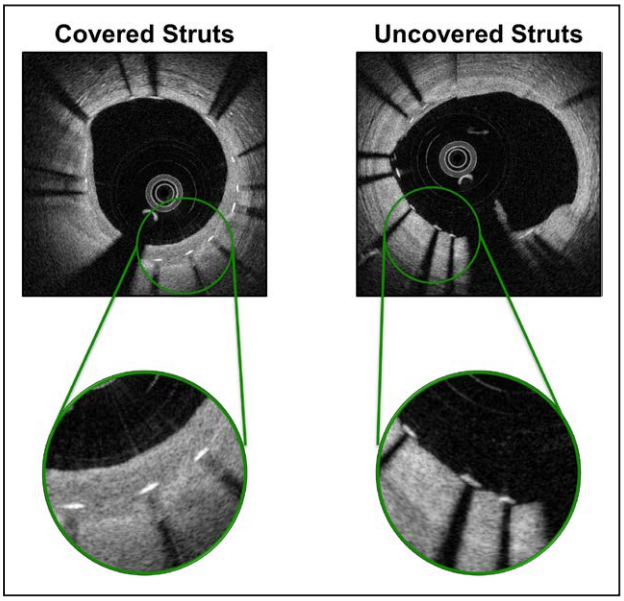

Figure 2. Optical frequency domain imaging shows covered struts (**left**) and uncovered struts (**right**).

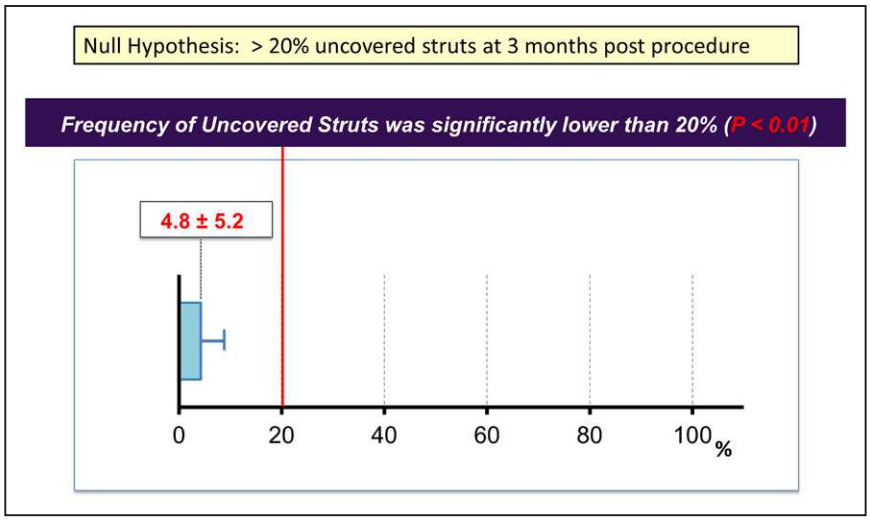

Figure 3. Optical frequency domain imaging–assessed percentage of uncovered struts at 3 months postprocedure in single implanted stents (primary end point) was 4.8%. The primary end point was reached (*P*<0.01) on the null hypothesis that uncovered struts were ≥20%.

hypertension, and 36.7% of patients presented with acute coronary syndrome (Table 1). The mean number of vessels diseased was 2.2±0.5, and mean number of lesions detected was 3.2±1.6 per patient. A total of 132 lesions were treated, with 1.4±0.6 lesions per patient treated at baseline and 1.1±0.4 lesions per patient treated at 1 month staged procedure, amounting to a total implanted stent length of 22.0±10.9 mm per lesion and 50.4±21.4 mm per patient (Table 1).

OFDI assessment was performed on 98% of lesions with 99% visualization success. Strut coverage at 3 months of single implanted stents (n=71), the primary end point of the study, was 95.2±5.2%. The combined single and overlapped stents showed similar coverage, which at 3 months was 95.4±4.9% (Figures 2 and 3). Strut coverage of combined single and overlapped stents at 1 (n=49) and 2 months (n=38) was 85.1±12.7% and 87.9±10.8%, respectively (Figures 4 and 5). The median neointimal hyperplasia thickness over covered struts was 0.04, 0.05, and 0.06 mm, whereas mean neointimal hyperplasia obstruction was 4.5±2.4%, 5.2±3.4%, and 6.6±3.3% at 1, 2, and 3 months, respectively (Figure 6). The frequency of malapposed struts per lesion over time was 1.7±2.6%, 1.3±2.2%, and 0.69±1.2% (Table 2). The in-stent late lumen loss for the Ultimaster stent was 0.04±0.3 mm at 3 months of follow-up. Complete angiographic follow-up of all lesions is reported in Table 3. A paired lesion analysis in 43 paired lesions at 0, 1, and 3 months were presented in Table I in the Data Supplement.

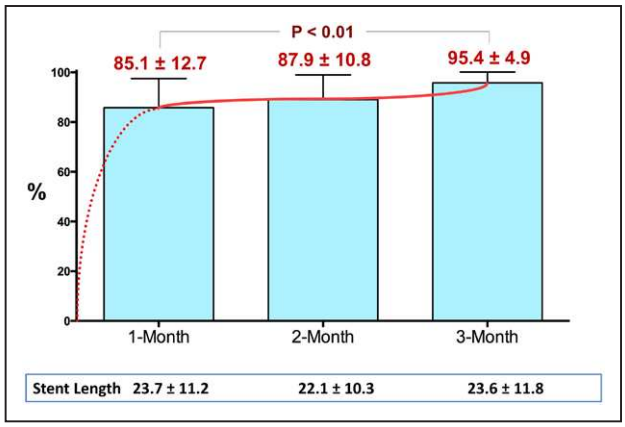

Figure 4. Frequency of strut coverage of combined both single and overlapped stents at 1, 2, and 3 months.

At 3-month follow-up, there were no deaths, whereas there were 3 non–Q-wave myocardial infarctions, 1 target lesion revascularization, and 1 target vessel revascularization. One patient experienced subacute ST because of a large stent malapposition left untreated. One-year clinical follow-up showed no occurrence of death with 2 additional target lesion revascularization (Table 4).

Discussion

To the best of our knowledge, this study is the first serial intravascular imaging evaluation of strut coverage very early (1–3 months) after DES implantation. The main findings of our study are the following: (1) a high level of strut coverage of the Ultimaster stent at 1-month OFDI follow-up; (2) an increase between 1 and 3 months of neointimal area and thickness, leading to a favorable strut coverage at 3 months evaluation; (3) a progressive reduction of strut malapposition; and (4) a good 1-year safety and efficacy profile of the Ultimaster stent in this complex multivessel diseased patient group. This study improves our insight into endothelial embedding of metallic DES. Ongoing randomized trials will investigate the clinical significance of this unique sequential OFDI finding by applying very short duration of DAPT.

Consistency With Previous Ultimaster Study

DISCOVERY 1TO3 shows consistent results with the first-in-man prospective CENTURY trial on the Ultimaster BP-SES.[12] Angiographic late loss at 6 months was 0.04±0.35 mm in the CENTURY trial compared with 0.04±0.30 mm in our study. The mean strut coverage assessed by OCT was 96.2% with 1.67±4.02 malapposed stent struts in the CENTURY Trial at 6 months compared with 95.2±5.2% with 0.69±1.24% malapposed stent struts in the DISCOVERY 1TO3 at 3 months, respectively.[12]

The Ultimaster BP-SES has also shown safety and efficacy profiles similar to the randomized CENTURY II trial that compared the Ultimaster BP-SES stent with the durable polymer everolimus-eluting stent (DP-EES).[13] Although the study enrolled patients with complex multivessel disease, the results of the DISCOVERY 1TO3 were consistent with the CENTURY II results.[13] The freedom from target lesion failure at 9 months

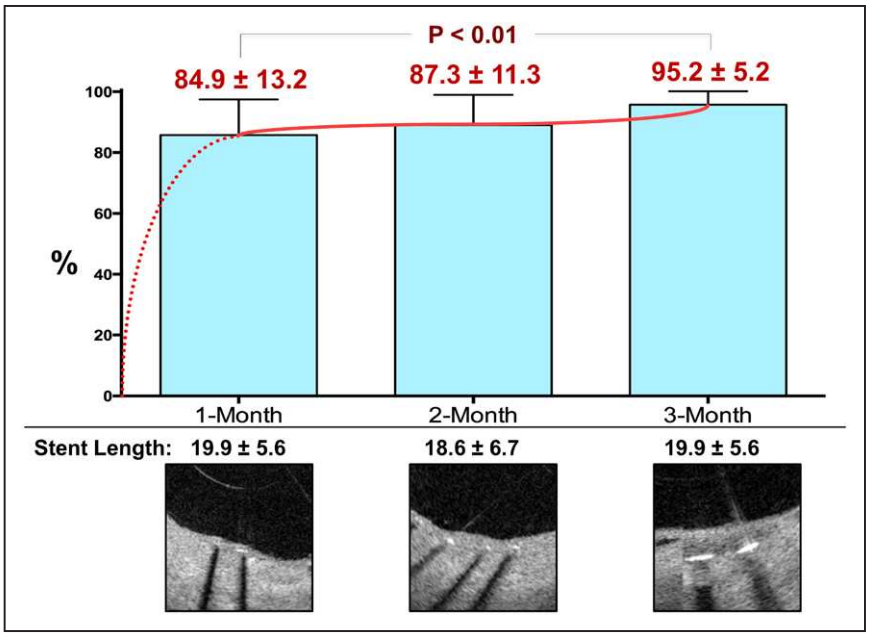

Figure 5. Frequency of strut coverage of single stents at 1, 2, and 3 months.

with the Ultimaster stent was 95.6% in the CENTURY II trial versus 91.7% at 12 months in DISCOVERY 1TO3 trial. Target vessel revascularization was 4.5% in the CENTURY II trial versus 5.1% in the DISCOVERY 1TO3. The ST rate was 0.9% and 1.7% in CENTURY II and DISCOVERY 1TO3, respectively.[13]

Strut Coverage in Second-Generation DES

OFDI has gained popularity and is frequently used to study pattern of vessel healing after DES implantation and also to assess potential underlying mechanisms for adverse events.

In a systematic review of strut coverage of different DES assessed by OFDI at 6 months, the first-generation sirolimus-eluting Cypher stent and paclitaxel-eluting Taxus stent showed 10.86% and 5.49% of uncovered struts, respectively.[17] At 9 months, Xience DP-EES had a 3.12% rate of uncovered struts.[17] The Ultimaster BP-SES stent, abluminally coated with sirolimus in a dose (3.9 µg/mm) less than half of those coated on Cypher stent, achieved similar rates of uncovered struts of 3.8% and 4.8% at 6 and 3 months, in the CENTURY and DISCOVERY 1TO3, respectively. The result achieved with zotarolimus-eluting durable polymer (Endeavor Resolute) and DP-EES (Xience) stents showed coverage rates of 92.6% and 94.2%, respectively, at 13 months in the RESOLUTE all-comer trials.[15] The BP-SES Ultimaster stent achieved similar coverage of 95.2% at a remarkably shorter duration of 3 months.

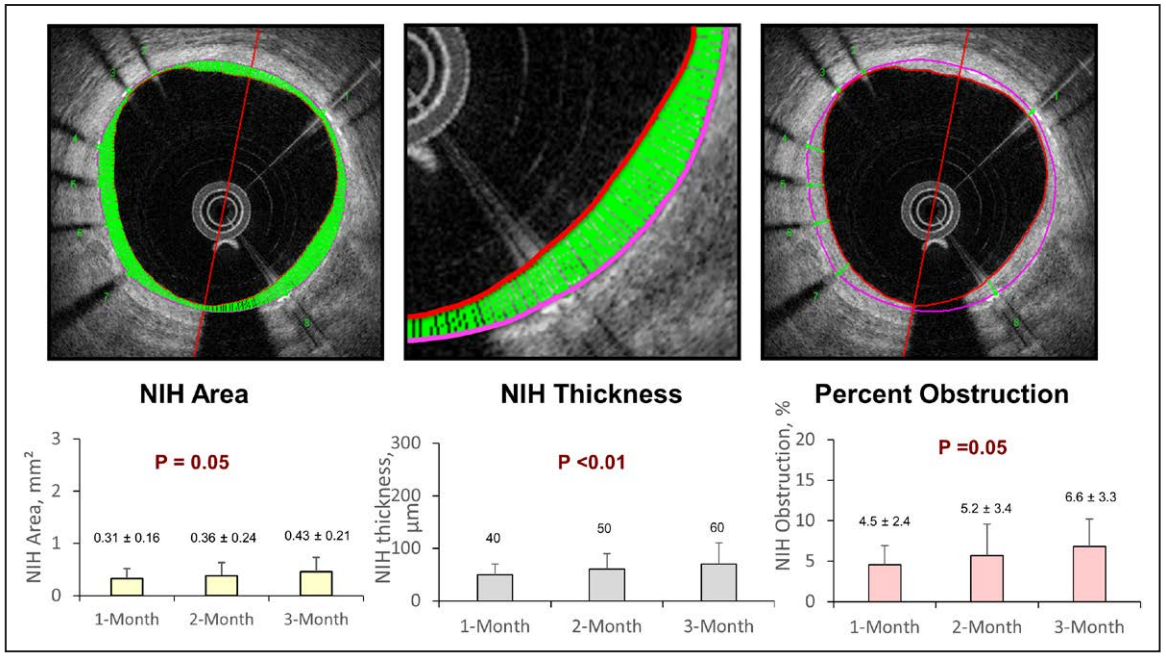

Figure 6. Optical frequency domain imaging (OFDI) efficacy end points show neointimal hyperplasia (NIH) area (**left**), NIH thickness (**middle**), and percentage of obstruction (**right**).

Table 2. OFDI Strut-Level Analysis: Single-Stented Lesions

	Primary Lesions				Staged Lesions		
	0 mo (n=62 Lesions)	1 mo (n=41 Lesions)	3 mo (n=60 Lesions)	*P* Value*	0 mo (n=29 Lesions)	2 mo (n=32 Lesions)	*P* Value
Analyzed stent length, mm	19.5±6.2	19.9±5.6	19.9±5.6	0.12	18.1±5.2	18.6±6.7	0.72
Mean stent area, mm^2	6.7±2.1	6.9±2.5	7.0±2.2†	0.03	6.9±2.4	7.2±2.5	0.27
Minimum stent area, mm^2	5.5±1.9	5.7±2.2	5.8±2.1†	0.01	5.7±2.2	6.0±2.2	0.01
Mean stent diameter, mm	2.9±0.4	2.9±0.5	2.9±0.5†	0.03	2.9±0.5	3.0±0.5	0.12
Stent volume, mm^3	128.0±55.3	135.6±60.3	135.0±60.6†	0.05	117.6±45.8	127.0±67.6	0.51
Mean lumen area, mm^2	6.8±2.0	6.9±2.4	6.7±2.3†	0.03	7.1±2.4	7.1±2.5	0.15
Minimum lumen area, mm^2	5.5±1.7	5.5±2.2	5.4±2.1†	0.01	5.8±2.1	5.8±2.3	0.46
Mean lumen diameter, mm	2.9±0.4	2.9±0.5	2.9±0.5†	0.03	2.9±0.5	2.9±0.6	0.11
Lumen volume, mm^3	129.8±54.7	134.2±59.6	130.2±59.7	0.79	121.1±45.4	125.2±66.7	0.26
Mean NIH area, mm^2	…	0.3±0.2	0.4±0.2	0.05‡	…	0.4±0.2	N/A
Mean NIH thickness, μm	…	40 [40–50]	60 [50–70]	<0.01‡	…	50 [40–70]	N/A
Percent NIH obstruction, %	…	4.5±2.4	6.6±3.3	0.05	…	5.2±3.4	N/A
Frequency of malapposed struts, %	5.3±5.25	1.67±2.59§	0.69±1.24†‖	<0.01	8.1±8.8	1.3±2.2	<0.01
Frequency of cross sections with >30% uncovered struts, %, median [IQR]	…	13.0 [2.0–24.5]	0.00 [0.0–3.4]	<0.01‡	…	9.5 [0.0–17.9]	N/A
Maximum length of consecutive segments of uncovered struts, mm, median [IQR]	…	3.7 [2.0–7.2]	1.4 [1.0–2.2]	<0.01‡	…	3.5 [1.8–4.7]	N/A
Maximum length of consecutive segments of malapposed struts, mm, median [IQR]	1.9 [0.98–3.6]	0.5 [0.0–0.6]§	0.4 [0.0–0.6] †‖	<0.01	2.1 [0.0–1.0]	0.6 [0.0–1.0]	<0.01

N/A indicates not applicable; NIH, neointimal hyperplasia; and OFDI, optical frequency domain imaging.
*For the serial comparisons among 0, 1, and 3 months (or any other comparison you want to provide).
†*P*<0.05 for the comparison of 3 vs 0 months.
‡For the comparison between 1 and 3 months.
§*P*<0.05 for the comparison between 1 and 0 months.
‖*P*<0.05 for the comparison between 3 and 1 months.

Guagliumi et al[18] showed similarly a low rate of strut malapposition of 1.51% and 1.80% with the benchmark Promus DP-EES and Xience DP-EES stents at 6 months, respectively. We report the lowest frequency of malapposed struts of 0.69% to date at 3 months for a DES. Indeed, the percentage of uncovered and malapposed struts was surprisingly low at 3 months compared with previous studies.[14,19]

At 9-month follow-up, an OCT substudy of CENTURY II trial showed excellent tissue coverage and apposition of both BP-SES and DP-EES.[20] Rate of uncovered struts at 9 months was 1.02% and 2.26%, respectively, with a similar rate of malapposed struts of 0.10% and 0.11%, respectively, in BP-SES and EES groups.

Incomplete vascular healing characterized by the presence of struts not covered by neointima and malapposed struts was found more frequent with BP-BES (Nobori) compared with DP-EES in 1 substudy of NEXT trial.[14] There have been concerns on the potential inflammatory response because of the shorter elution than polymer absorption time of BP-BES. Compared with BP-BES, BP-SES has fundamental distinctive features in terms of stent alloy (cobalt-chromium versus stainless steel), strut thickness (80 versus 120 μm), and drug kinetic release/polymer absorption time ratio. These differences are believed to translated into the high rate of strut coverage and low malapposition rates observed in the present study with the Ultimaster BP-SES stent.

We can ascertain that the unique design of this study using a sequential OFDI analysis at 1, 2, and 3 months of treated lesions demonstrated that strut coverage of the BP-SES Ultimaster stent occurs mainly within the first month with minor but significant increase, between 1 and 3 months. DISCOVERY 1TO3 study reached its primary end point with only 4.8% uncovered struts in both single and multiple stented lesions at 3 months, despite the high complexity of patients/lesions.

Strut Coverage Versus Endothelialization

Preclinical studies have shown that strut coverage evaluated by OFDI or OCT can correspond to neointima formation, fibrin accumulation, or high rates of active inflammation. Although Templin et al[11] have shown a fine detection of neointimal coverage using OFDI on animal model and Nakano et al[21] have found a better detection of strut coverage with OFDI than IVUS, the correlation between strut coverage and recovery of endothelial function is still unclear.

Soucy et al[22] found a high contribution (86%–96%) of endothelial cells to the strut coverage in animal models after bare-metal stent and DES implantations, whereas in Malle et al,[23] a low rate of maturity in neointimal tissue was reported. In a short series, Murase et al[24] described an association between coverage homogeneity and quality of response

Table 3. QCA Analysis in All Lesions

	Pre	Post	1 mo	3 mo	*P* Value
Group 1–3 mo, Primary	n=80	n=80	n=52	n=68	1 vs 3 mo
RVD (in lesion/in stent), mm	2.5±0.5	2.81±0.46	2.78±0.44	2.83±0.46	0.04
Lesion length, mm	14.3±6.9	…	…	…	…
DS (lesion/in stent), %	70±13	11±6	11±6	13±7	NS
MLD (in stent), mm	0.7±0.3	2.5±0.4	2.5±0.4	2.5±0.4	NS
Acute gain (in stent), mm	…	1.8±0.5	…	…	…
Late loss (in stent), mm	…	…	0.07±0.3	0.04±0.3	NS
Late loss (in segment), mm	…	…	0.01±0.5	0.04±0.4	NS
	Pre	Post	2 mo		*P* Value
	n=44	n=44	n=41		post vs 2 m
RVD (in lesion/in stent), mm	2.5±0.5	2.8±0.6	2.8±0.5		NS
Lesion length, mm	13.6±7.1	…	…		…
DS (lesion/in stent), %	58±15	11±6	13±6		0.04
MLD (in stent), mm	1.1±0.5	2.5±0.4	2.5±0.5		NS
Acute gain (in stent), mm	…	1.4±0.5	…		…
Late loss (in stent), mm	…	…	0.02±0.3		…
Late loss (in segment), mm	…	…	–0.09±0.4		…

to acetylcholine test. On the contrary, Won et al[25] found an absence of correlation in a group of 112 patients.

Strut Coverage and DAPT Duration

Human autopsy studies reveal that incomplete healing as evidenced by uncovered stent struts is the most powerful predictor of late ST.[26] Furthermore, the presence of >30% uncovered struts was identified to be highly predictive of ST after DES implantation.[27]

Taniwaki et al[28] used OCT to examine 64 patients who developed very late ST during a median of 5-year follow-up after their index procedures. A believed cause for the events was identified using OCT for 98% of cases, including strut malapposition (34.5%) and uncovered struts (12.1%). Moreover, uncovered and malapposed struts were more common in the thrombosed regions. Guagliumi et al[27] also identified uncovered struts as the most common OCT correlate of ST. In another study, Kim et al[29] showed that the uncovered group was more likely to have complex lesions, smaller reference vessel and stent diameter, longer stent, more use of sirolimus-eluting stents, and less use of zotarolimus-eluting stents compared with the covered group. Contrary, Murakami et al[30] described an absence of correlation between neointimal growth and absence of thrombosis.

This debate on the protective effect of homogeneous coverage obtained as early as 1 month in DISCOVERY 1TO3 trial paves the way to the initiation of an abbreviated DAPT study. This will be evaluated by the MASTER DAPT trial which will enroll 4300 high bleeding risk patients receiving the Ultimaster stent. Post-stent implantation, patients will be randomized to receive either guideline-recommended standard DAPT treatment or transitioned to APT monotherapy, following 1 month of postprocedure DAPT treatment for all patients.

Table 4. Clinical Outcomes

	1 mo	1–3 mo	3 mo to 1 y
Death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
MI, n (%)	3 (5.1)	0 (0.0)	0 (0.0)
TLR, n (%)	1 (1.7)	0 (0.0)	2 (3.4)
TVR, non-TLR, n (%)	1 (1.7)	0 (0.0)	0 (0.0)
Non-TVR, n (%)	1 (1.7)	0 (0.0)	0 (0.0)
TLF, n (%)	3 (5.1)	0 (0.0)	2 (3.4)
ST, n (%)*	1 (1.7)	0 (0.0)	0 (0.0)

MI indicates myocardial infarction; ST, stent thrombosis; TLF, target lesion failure; TLR, target lesion revascularization; and TVR, target vessel revascularization.

*ST subacute followed by MI because of large untreated stent malapposition.

Limitations

There are several limitations in the present study. First, this study included a small study population in a prospective and nonrandomized study. Therefore, selection bias may exist in the present study which might have biased the conclusion. Second, the trial was powered for the OFDI end point and as such, because of a small number of patients, does not allow the drawing of any conclusions on clinical outcomes. Although strut coverage could guide DAPT therapy duration, little is known about the correlation between minimal percentage strut coverage, the quality of the coverage tissues, and optimal DAPT duration, and whether this can influence clinical outcome without conducting a randomized study addressing the issue.

Conclusions

In this complex patient population, our study demonstrates rapid strut coverage of the Ultimaster DES, with the majority

of strut coverage process taking place within the first month after stent implantation. The unique sequential OFDI analysis at 1, 2, and 3 months of treated lesions improves our insight into the embedding of novel metallic BP-DES and paves the way for a large-scale randomized trial assessing its clinical relevance.

Sources of Funding

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Disclosures

Dr Chevalier is a consultant for Terumo; Dr Mehilli receives lecture fees from Abbott Vascular, BMS, Lilly/Daiichi Sankyo, Edwards Lifescience, Terumo institutional research grant, Abbott Vascular, and Edwards Lifescience. The other authors report conflicts except the research grant received in the frame of the DISCOVERY 1TO3 study.

References

1. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, Fusaro M, Schneider S, Schulz S, Ibrahim T, Ott I, Massberg S, Laugwitz KL, Kastrati A. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. *JACC Cardiovasc Interv*. 2013;6:1267–1274. doi: 10.1016/j.jcin.2013.06.015.
2. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193–202. doi: 10.1016/j.jacc.2006.03.042.
3. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS) [published online ahead of print August 26, 2017]. *Eur Heart J*. doi: 10.1093/eurheartj/ehx419.
4. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation*. 2004;109:701–705. doi: 10.1161/01.CIR.0000116202.41966.D4.
5. Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, Jüni P, Schömig A, Windecker S, Kastrati A. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J*. 2012;33:1214–1222. doi: 10.1093/eurheartj/ehs086.
6. Chevalier B, Wijns W, Silber S, Garcia E, Serra A, Paunovic D, Serruys P; NOBORI 1 Investigators. Five-year clinical outcome of the Nobori drug-eluting coronary stent system in the treatment of patients with coronary artery disease: final results of the NOBORI 1 trial. *EuroIntervention*. 2015;11:549–554. doi: 10.4244/EIJY14M12_13.
7. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation*. 2016;134:e123–e155. doi: 10.1161/CIR.0000000000000404.
8. Motreff P, Souteyrand G. Optical coherence tomography to diagnose under-expansion of a drug-eluting stent. *JACC Cardiovasc Imaging*. 2009;2:245–246; author reply 246. doi: 10.1016/j.jcmg.2008.11.008.
9. Tanigawa J, Barlis P, Di Mario C. Intravascular optical coherence tomography: optimisation of image acquisition and quantitative assessment of stent strut apposition. *EuroIntervention*. 2007;3:128–136.
10. Suzuki Y, Ikeno F, Koizumi T, Tio F, Yeung AC, Yock PG, Fitzgerald PJ, Fearon WF. In vivo comparison between optical coherence tomography and intravascular ultrasound for detecting small degrees of in-stent neointima after stent implantation. *JACC Cardiovasc Interv*. 2008;1:168–173. doi: 10.1016/j.jcin.2007.12.007.
11. Templin C, Meyer M, Müller MF, Djonov V, Hlushchuk R, Dimova I, Flueckiger S, Kronen P, Sidler M, Klein K, Nicholls F, Ghadri JR, Weber K, Paunovic D, Corti R, Hoerstrup SP, Lüscher TF, Landmesser U. Coronary optical frequency domain imaging (OFDI) for in vivo evaluation of stent healing: comparison with light and electron microscopy. *Eur Heart J*. 2010;31:1792–1801. doi: 10.1093/eurheartj/ehq168.
12. Barbato E, Salinger-Martinovic S, Sagic D, Beleslin B, Vrolix M, Neskovic AN, Jagic N, Verheye S, Mehmedbegovic Z, Wijns W. A first-in-man clinical evaluation of Ultimaster, a new drug-eluting coronary stent system: CENTURY study. *EuroIntervention*. 2015;11:541–548. doi: 10.4244/EIJY14M08_06.
13. Saito S, Valdes-Chavarri M, Richardt G, Moreno R, Iniguez Romo A, Barbato E, Carrie D, Ando K, Merkely B, Kornowski R, Eltchaninoff H, James S, Wijns W; CENTURY II Investigators. A randomized, prospective, intercontinental evaluation of a bioresorbable polymer sirolimus-eluting coronary stent system: the CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease) trial. *Eur Heart J*. 2014;35:2021–2031. doi: 10.1093/eurheartj/ehu210.
14. Kubo T, Akasaka T, Kozuma K, Kimura K, Fusazaki T, Okura H, Shinke T, Ino Y, Hasegawa T, Takashima H, Takamisawa I, Yamaguchi H, Igarashi K, Kadota K, Tanabe K, Nakagawa Y, Muramatsu T, Morino Y, Kimura T; NEXT Investigators. Vascular response to drug-eluting stent with biodegradable vs. durable polymer. Optical coherence tomography substudy of the NEXT. *Circ J*. 2014;78:2408–2414. doi: 10.1253/circj.CJ-14-0337.
15. Gutiérrez-Chico JL, van Geuns RJ, Regar E, van der Giessen WJ, Kelbæk H, Saunamäki K, Escaned J, Gonzalo N, di Mario C, Borgia F, Nüesch E, García-García HM, Silber S, Windecker S, Serruys PW. Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. a fluoropolymer-coated everolimus-eluting stent at 13-month follow-up: an optical coherence tomography substudy from the RESOLUTE All Comers trial. *Eur Heart J*. 2011;32:2454–2463. doi: 10.1093/eurheartj/ehr182.
16. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351. doi: 10.1161/CIRCULATIONAHA.106.685313.
17. Papayannis AC, Cipher D, Banerjee S, Brilakis ES. Optical coherence tomography evaluation of drug-eluting stents: a systematic review. *Catheter Cardiovasc Interv*. 2013;81:481–487. doi: 10.1002/ccd.24327.
18. Guagliumi G, Capodanno D, Ikejima H, Bezerra HG, Sirbu V, Musumeci G, Fiocca L, Lortkipanidze N, Vassileva A, Tahara S, Valsecchi O, Costa MA. Impact of different stent alloys on human vascular response to everolimus-eluting stent: an optical coherence tomography study: the OCTEVEREST. *Catheter Cardiovasc Interv*. 2013;81:510–518. doi: 10.1002/ccd.24374.
19. Inoue T, Shite J, Yoon J, Shinke T, Otake H, Sawada T, Kawamori H, Katoh H, Miyoshi N, Yoshino N, Kozuki A, Hariki H, Hirata K. Optical coherence evaluation of everolimus-eluting stents 8 months after implantation. *Heart*. 2011;97:1379–1384. doi: 10.1136/hrt.2010.204339.
20. Kuramitsu S, Kazuno Y, Sonoda S, Domei T, Jinnouchi H, Yamaji K, Soga Y, Shirai S, Ando K, Saito S. Vascular response to bioresorbable polymer sirolimus-eluting stent vs. permanent polymer everolimus-eluting stent at 9-month follow-up: an optical coherence tomography sub-study from the CENTURY II trial. *Eur Heart J Cardiovasc Imaging*. 2016;17:34–40. doi: 10.1093/ehjci/jev203.
21. Nakano M, Vorpahl M, Otsuka F, Taniwaki M, Yazdani SK, Finn AV, Ladich ER, Kolodgie FD, Virmani R. Ex vivo assessment of vascular response to coronary stents by optical frequency domain imaging. *JACC Cardiovasc Imaging*. 2012;5:71–82. doi: 10.1016/j.jcmg.2011.09.015.

22. Soucy NV, Feygin JM, Tunstall R, Casey MA, Pennington DE, Huibregtse BA, Barry JJ. Strut tissue coverage and endothelial cell coverage: a comparison between bare metal stent platforms and platinum chromium stents with and without everolimus-eluting coating. *EuroIntervention*. 2010;6:630–637. doi: 10.4244/EIJV6I5A105.
23. Malle C, Tada T, Steigerwald K, Ughi GJ, Schuster T, Nakano M, Massberg S, Jehle J, Guagliumi G, Kastrati A, Virmani R, Byrne RA, Joner M. Tissue characterization after drug-eluting stent implantation using optical coherence tomography. *Arterioscler Thromb Vasc Biol*. 2013;33:1376–1383.
24. Murase S, Suzuki Y, Yamaguchi T, Matsuda O, Murata A, Ito T. The relationship between re-endothelialization and endothelial function after DES implantation: comparison between paclitaxcel eluting stent and zotarolims eluting stent. *Catheter Cardiovasc Interv*. 2014;83:412–417. doi: 10.1002/ccd.25140.
25. Won H, Kim JS, Shin DH, Kim BK, Ko YG, Choi D, Jang Y, Hong MK. Relationship between endothelial vasomotor function and strut coverage after implantation of drug-eluting stent assessed by optical coherence tomography. *Int J Cardiovasc Imaging*. 2014;30:263–270. doi: 10.1007/s10554-013-0325-4.
26. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation*. 2007;115:2435–2441. doi: 10.1161/CIRCULATIONAHA.107.693739.
27. Guagliumi G, Sirbu V, Musumeci G, Gerber R, Biondi-Zoccai G, Ikejima H, Ladich E, Lortkipanidze N, Matiashvili A, Valsecchi O, Virmani R, Stone GW. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. *JACC Cardiovasc Interv*. 2012;5:12–20. doi: 10.1016/j.jcin.2011.09.018.
28. Taniwaki M, Radu MD, Zaugg S, Amabile N, Garcia-Garcia HM, Yamaji K, Jørgensen E, Kelbæk H, Pilgrim T, Caussin C, Zanchin T, Veugeois A, Abildgaard U, Jüni P, Cook S, Koskinas KC, Windecker S, Räber L. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. *Circulation*. 2016;133:650–660. doi: 10.1161/CIRCULATIONAHA.115.019071.
29. Kim BK, Kim JS, Oh C, Ko YG, Choi D, Jang Y, Hong MK. Major determinants for the uncovered stent struts on optical coherence tomography after drug-eluting stent implantation. *Int J Cardiovasc Imaging*. 2012;28:705–714. doi: 10.1007/s10554-011-9896-0.
30. Murakami D, Takano M, Yamamoto M, Inami S, Ohba T, Seino Y, Mizuno K. Advanced neointimal growth is not associated with a low risk of in-stent thrombus. Optical coherence tomographic findings after first-generation drug-eluting stent implantation. *Circ J*. 2009;73:1627–1634.

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Serial Assessment of Strut Coverage of Biodegradable Polymer Drug-Eluting Stent at 1, 2, and 3 Months After Stent Implantation by Optical Frequency Domain Imaging: The DISCOVERY 1TO3 Study (Evaluation With OFDI of Strut Coverage of Terumo New Drug Eluting Stent With Biodegradable Polymer at 1, 2, and 3 Months)

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SUPPLEMENTAL MATERIALS

Serial assessment of strut coverage of biodegradable polymer DES at one, two and three months after stent implantation by optical frequency domain imaging: The DISCOVERY 1TO3 study

Expanded Methods: outline of study protocol

The primary purpose of the DISCOVERY1TO3 study is Optical Frequency Domain Imaging (OFDI) investigation of strut coverage of the sirolimus-eluting stent with biodegradable polymer at 1, 2 and 3 months after stent implantation. This study is the pilot study to assess feasibility of shorter dual antiplatelet therapy (DAPT) after PCI with this new stent.

Design
This study is a prospective, single arm, multicenter, open label study with adaptive design. All patients will undergo angiographic follow-up at 3 months, OFDI imaging after baseline and at 1, 2 and 3 months, and clinical follow-up at 1 year.
The primary endpoint is OFDI assessed percent stent strut coverage at 3 months post procedure.
Our hypothesis is that less than 20% uncovered struts at 3 months post procedure. The primary endpoint will be assessed for all single stent lesions.

Secondary endpoints include:

1. Number (%) of stent strut coverage at 1 and 2 months;
2. Number (%) of stented lesions which have >10 % uncovered stent struts at 1, 2 or 3 months;
3. Number (%) of stented lesions which have >20% uncovered struts at 1, 2 or 3 months;
4. Percentage of acquired malapposed struts at 1, 2 and 3 months;
5. Amount of in-stent intimal hyperplasia (mm^3) at 1, 2 and 3 months;
6. Amount of in-segment intimal hyperplasia (mm^3) at 1, 2 and 3 months;
7. Neo-intimal thickness (μm) at 3 months;
8. In-stent late-lumen loss at 3 months by QCA;
9. In-segment late lumen loss at 3 months by QCA;
10. Target Lesion Revascularization (TLR) at 1, 3, and 12 months post-procedure;
11. Target Vessel Revascularization (TVR) at 1, 3 and 12 months post-procedure;
12. Target Lesion Failure (TLF), composite endpoint of Cardiac Death, target vessel related Myocardial infarction (MI) and Clinically Indicated TLR at 1, 3 and 12 months postprocedure;
13. Major Cardiac Adverse Events (MACE) defined as cardiac death, MI (Q wave and non-Q wave), emergent coronary artery bypass surgery, or target vessel revascularization (TVR) at 1, 3 and 12 months post-procedure;

14. Stent thrombosis at 1, 3 and 12 months post-procedure;
NOTE: all secondary endpoints will be assessed for single stent lesions and overlapping stent lesions.

Study population
The study plans to enroll up to 60 patients with coronary multi-vessel disease, clinically indicated as candidates for staged multi-vessel PCI treatment of de novo lesions located in native coronary arteries. Number of patients will be decided by number of target lesions treated with single stent, assessable at 3 months follow-up, taking into account a 15% drop-out rate. Enrolment will be done in consecutive cohorts of 10 patients. Assessment of available lesions suitable for assessment at 3 months will be done per enrolment of patient cohort of 10 patients. Clinical sites are the following: Maasstad Ziekenhuis, Rotterdam; Erasmus MC, Rotterdam, MC Leeuwarden, Leeuwarden, the Netherlands; Institut Cardiovasculaire Paris Sud, Massy; CHU Rangueil, Toulouse. France; LMU München, Munich, Germany.

Inclusion Criteria are the following:
1. Patient is at least 18 years old;
2. Patients is a suitable candidate for PCI;
3. Patient has multi-vessel disease with ⩾2 de-novo lesions in native coronary arteries suitable for treatment with TCD-10023 DES;
4. Target lesions are suitable for OFDI examination;
5. Patient requires staged procedure between 3-5 weeks after baseline procedure, according to investigator's judgement;
6. Target vessel reference diameter is between 2.5 - 4.0 mm (visual assessment);
7. Patient has provided written informed consent;
8. Patient is affiliated to social security or equivalent system (France only).
Exclusion Criteria
1. Patient has known allergy to sirolimus, cobalt, chromium, nickel, or contrast agent (that cannot be adequately premedicated);
2. Patient is not a suitable candidate for use of DAPT because of active or recent bleedings or for use of vitamin K antagonist, like warfarin, dabigatran, rivaroxaban or acenocoumarol;
3. Patient is presenting with STEMI at baseline procedure;
4. Patient has Killip class > 1 at admission;
5. Patient is in cardiogenic shock;
6. Patient is a female of childbearing potential;
7. Patient has life expectancy of less than 1 year;
8. Patient is expected to undergo major surgery within 3 months;
9. Patient has Left Main disease ⩾ 50%;
10. Target lesion at bifurcation requiring 2 stents technique;
11. Target lesions are severely calcified;
12. Target lesion is aorta-ostially located (within 3 mm of vessel origin);

13. Patient has renal failure defined as estimated Glomerular Filtration Rate (eGFR) <50 mL/min/1.73m²;
14. Target lesions require preparation other than balloon pre-dilatation;
15. Patient is currently participating in an investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints;
16. In the Investigator's opinion patient has (a) co-morbid condition(s) that could limit the patient's ability to participate in the study, compliance with follow-up requirements or impact the scientific integrity of the study;
17. Patient is under judicial protection (France only).

Procedure

All potential patients must be consented prior to performing any study specific procedures. This study will utilize unique patient numbers for the purpose of trial data collection. The Case Report Form (CRF) will be electronic (eCRF) and a unique patient number will be automatically assigned. This study is performed as 'open label' study, no blinding will be applied. In baseline procedure, pre-dilatation can be performed at discretion of the investigator. More than one study stent can be used for elective treatment of a target lesion. Only study stents can be used.
Post dilatation is not mandatory and left at the discretion of the operator. If a satisfactory result has been obtained (<20% rest stenosis), OFDI procedure of the treated segments is done for control and images stored on hard disk. Staged procedures for treatment of multi vessel coronary artery disease are planned at 3-5 weeks post index procedure. A staged procedure should be electively planned at the end of the baseline procedure. Care should be taken to use only the study stent for treatment of all lesions. Patients will be receiving dual antiplatelet therapy until at least 6 months after the last Ultimaster stent implantation.

Follow-up

Enrolled patients will be followed for a period of 12 months after the index procedure.
Follow-up procedures for this study will include:

- Assessment of available documentation of referring physicians, including general practitioners as well as cardiologists and family members.
- Any change of medication since last contact should be documented in the eCRF including reason for change. Any suspension or interruption of DAPT (ASA, clopidogrel and/or prasugrel or other antiplatelet drug) should be documented in the patient's records and the case report forms.
- ECG if available.

A clinical assessment will include:

- Angina status after procedure before discharge.
- All adverse events (serious and non-serious) occurring since procedure.
- Concomitant medications.

Follow up is scheduled at 3-months post-procedure (±14 days) and 12 months (±30 days). 3 months follow up will include clinical follow up with hospital (site) visit and angiographic & OFDI follow up. 12 months follow up will be hospital visit or telephone contact. If in-between protocol required visits/telephone contacts, the site study team learns of any adverse events, the available relevant information should be captured on the appropriate eCRF page.

Clinical events and reporting

In this study, patients should be encouraged to report AEs spontaneously or in response to general, non-directed questioning. If it is determined that an AE has occurred, the Investigator should obtain all the information required to complete the AE page of the eCRF. In addition, patients will be instructed to contact the Investigator, and/or study coordinator if any adverse events occur between study evaluation visits. The Investigator will record the nature, severity, treatment and outcome of the AE, and will determine the relationship to the investigational products, study mandated medications or any CIP mandated procedures involved in the clinical study.

SUPPLEMENTAL MATERIAL

Data Supplement Table 1: OFDI paired lesion analysis (n=43 pairs)

	0-Month	1-Month	3-Month	P-Value*
Analyzed stent length, mm	24.5 ± 12.8	23.8 ± 11.8	24.6 ± 14.0	0.16
Mean stent area, mm^2	7.11 ± 2.58	7.24 ± 2.64	7.19 ± 2.51	<0.01
Min. stent area, mm^2	5.8 ± 2.3	5.92 ± 2.36	5.93 ± 2.32	<0.01
Mean stent diameter, mm	2.96 ± 0.53	2.98 ± 0.54	2.98 ± 0.51	0.01
Stent volume, mm^3	169.1 ± 102.6	170.6 ± 110.8	169.8 ± 104.6	0.09
Mean lumen area, mm^2	7.22 ± 2.51	7.14 ± 2.58	6.98 ± 2.49	<0.01
Min. lumen area, mm^2	5.8 ± 2.16	5.71 ± 2.32	5.43 ± 2.31	<0.01
Mean lumen diameter, mm	2.99 ± 0.51	2.96 ± 0.53	2.93 ± 0.51	<0.01
Lumen volume, mm^3	172 ± 103.89	168.53 ± 108.9	163.7 ± 97.2	0.49
Mean NIH area, mm^2	-	0.34 ± 0.19	0.43 ± 0.3	<0.017
Mean NIH thickness, µm		40	60	<0.01
Percent NIH obstruction, %	-	4.76 ± 2.42	6.08 ± 3.34	<0.01
Frequency of malapposed struts, %	5.75 ± 5.59	1.79 ± 2.65	1.79 ± 2.65	<0.01
Frequency of cross-sections with>30% uncovered struts, %, median [IQR]	-	12.1 [1.7 – 24.6]	0 [0 – 3.8]	<0.01
Maximum length of consecutive segments of uncovered struts, mm, median [IQR]	-	4.6 [2.1 - 7.4]	1.9 [1.1 - 2.7]	<0.01

ANGIOGRAPHIC CORELAB: CERC, Massy, France

OFDI: CRC, Sao Paulo, Brazil – Dr Daniel Chamié

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